

Research Protocol

The effect of acupuncture on hemodialysis patients with restless legs syndrome(RLS)

Version 8-23-2019

Principal Investigator:

Principal Investigator(s): Jia-Ming Chen

Institution: CHANGHUA CHRISTIAN HOSPITAL, TAIWAN

Protocol No. : Y_105_0300 / CCH IRB No. : 170217

Date of Approval: Aug 23, 2019

Address: 135 Nanxiao St., Changhua City, Changhua County 500, Taiwan (R.O.C.)

Tel: 886-4-723-8595

The effect of acupuncture on hemodialysis patients with restless legs syndrome(RLS) study protocol for a randomized crossover trial

I. Study Objectives

To our knowledge, there have been no studies on the impact of acupuncture therapy on RLS in patients undergoing hemodialysis. Therefore, the present study was conducted to determine the effect of acupuncture on the severity of RLS in hemodialysis patients. The study is a randomized crossover trial.

II. Background and Rationale

Restless legs syndrome (RLS), a common sensorimotor movement disorder first described in detail by Ekbom, ranges in severity from merely causing annoyance in the patient to affecting sleep and quality of life severely enough to warrant medical treatment. Remarkable differences in prevalence rates of RLS can be observed across countries and geographic regions. Epidemiological research demonstrates that the prevalence of RLS in adults (18 years or more) ranges from less than 1% in Singapore to approximately 10% in Europe and the United States. In 1995, a uniform diagnosis of RLS was made possible worldwide, based on the criteria proposed by the International RLS Study Group (IRLSSG). According to the most recently revised diagnostic criteria, the four clinical manifestations mandatory for the diagnosis are:

- (1) an urge to move the legs, accompanied or caused by uncomfortable and unpleasant sensations in the legs;
- (2) the urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity;
- (3) the urge to move or the unpleasant sensations are partially or totally relieved by movement;
- (4) the urge to move or the unpleasant sensations are worse in the evening or night or only occur in the evening or night.

Acupuncture, an ancient Chinese medical therapy used in the prevention and treatment of disease, is another useful method for treating RLS. It involves inserting needles into specific points (acupoints or Xue Wei) on the human body to bring about its therapeutic effects. Conventional science suggests that acupuncture works by neurological, neurohormonal as well as psychological mechanisms, and it is thought to confer an analgesic effect. Several kinds of acupuncture methods, such as body acupuncture, auricular acupuncture, scalp acupuncture, electro-acupuncture, laser

acupuncture, acupressure, acupoint injection therapy (injection of drugs into acupoints) or a combination of the approaches mentioned above, are used in the treatment of RLS.

The mechanism of acupuncture treatment for RLS is still ill-defined. According to our preliminary research, the current practice of acupuncture for RLS is mainly based on principles of Traditional Chinese Medicine (TCM) rather than conventional science. The traditional explanation, based on TCM theory, is that acupuncture restores the balance between Yin and Yang and regulates Qi (the essence) and blood so that integral unity can be maintained and miscellaneous diseases cured.

The development of this disorder in hemodialysis patients is progressive, affecting various physical and psychological dimensions over time. The symptoms of this syndrome are greatly intensified at rest, and are relieved by moving the extremities, especially the legs. In hemodialysis patients, the symptoms mainly occur during dialysis when the patient is at rest and cause discomfort. Evidence suggests that RLS in hemodialysis patients is associated with a risk of cardiovascular disease, osteoporosis, musculoskeletal pain, and increased mortality. In the general population and in patients with end-stage renal disease (ESRD), the potential causes of RLS include anemia, pregnancy, iron deficiency, the dysfunction of dopamine within the central nervous system, a family history of RLS, and peripheral neuropathy. In patients with ESRD, iron deficiency, anemia, and dialysis are predisposing factors that can lead to RLS.

Some clinical trials have examined the efficacy of acupuncture in the treatment of RLS and demonstrated that it was able to alleviate the clinical symptoms. To our knowledge, however, there have been no studies on the impact of acupuncture therapy on RLS in patients undergoing hemodialysis. Therefore, the present study was conducted to determine the effect of acupuncture on the severity of RLS in hemodialysis patients.

III. Procedures

A. Research and Design

Subject Selection/Sample

Inclusion criteria:

- 1) Patients between 18-80 years old diagnosed with RLS in hemodialysis patients according to the diagnostic criteria of the International Restless Legs Syndrome Study Group (11).
- 2) Subjects should have bothersome RLS symptoms, despite best medical therapy

- 3) Subjects should be stable on all RLS medication for at least 4 weeks prior to enrollment
- 4) All subjects must be able to read and write in English in order to be able to complete home diary cards and questionnaires.
- 5) All women of childbearing age must be using an acceptable form of birth control, including abstinence, IUD or intrauterine system in place for at least 3 months prior to screening, subject or partner using barrier method (e.g., condom, diaphragm, or cervical cap) with spermicide from screening through study completion; partner has a documented vasectomy > 6 months prior to Baseline, Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to screening.

Exclusion criteria:

- 1) RLS secondary associated with end stage renal disease, iron deficiency or pregnancy
- 2) Does not have sufficient vision to be compliant with study procedures.
- 3) Any other condition (other than the primary indications), which in the opinion of the investigators might contribute to difficulty complying with the protocol

B. Measurement/Instrumentation

- 1) International Restless Legs Severity Scale (12): a 40 point scale measuring severity of restless leg symptoms. Patients are asked to answer a series of 10 questions each of which have values ranging from 0 to 4 and the points are then added. Higher values are associated with more severe symptoms.
- 2) Insomnia Severity Index: a series of 7 questions assessing quality of sleep, with values ranging from 0 to 28.
- 3) heart rate variability: HRV is the measure of the inconsistent gaps between each heartbeat and is used as an index for different aspects of psychology. HRV is an index of the influence of both the parasympathetic nervous system and the sympathetic nervous systems.

Outcome measures will be at baseline and at week 4,10 and 18. Medical history including demographic information and information about alcohol, drug and tobacco use will be collected at the baseline visit. Medications and vital signs will be recorded at each visit. Adverse events will be recorded at week 4,10 and 18 or as reported by the patients. Anticipated benefits for the subjects in the treatment arms will be attenuation of RLS symptoms and improvement in quality of life and sleep.

Statistical Considerations:

A. Sample Size:

A total of 60 patients will be accrued to the study with roughly equal allocation to each treatment arm. This sample size will achieve over 90% power to detect a 5 point change in the International Restless Legs Severity Scale for the main effects of acupuncture assuming a standard deviation of 4 within each cohort. Additionally we will have roughly 80% power to detect a potential interaction effect on acupuncture therapy. Every effort will be made to reduce attrition; consent documents will emphasize the importance of complete data and encourage patients to return for the follow-up visit.

B. Randomization:

Patients will be randomized to one of the two treatment options with equal allocation. In an attempt to balance severity across treatment cohorts the randomization scheme will be stratified by baseline severity of RLS symptoms as measured by the International Restless Legs Severity Scale (severe vs. very severe). The randomization scheme will be generated by the study statistician with varying block sizes and uploaded to a web-based randomization program. After the patients eligibility has been confirmed and consent documents signed the research coordinator will randomize the patient to one of the two treatment options via the web-based randomization program. The PI will not randomize patients or have access to their treatment assignments.

C. Analysis plan:

All demographic and baseline characteristics of interest will be summarized both overall and by cohort. Frequencies and percentages will be used to summarize categorical variables and means, standard deviations and other appropriate measures of spread for continuous variables. ANOVA models will be used for testing and to estimate the effects of acupuncture. Sensitivity analyses may be considered to assess the impact of baseline severity and other clinically relevant covariates on the outcomes. We will adjust for multiplicity for all contrasts. Secondary outcomes will be analyzed using a similar approach. Further details will be provided in the Statistical Analysis Plan (SAP). For study-related patient data (case report forms) a unique identifier will be used. Study-related documents will be kept in a locked cabinet in a locked office. A separate list (paper-only) will be made containing the unique identifier and the name of each participant. This list will be kept separate from the study related documents. Study databases will be stored on a password protected computer network in a locked office and kept for 5 years.

IV. Bibliography

References

1. Salminen AV, Rimpila V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). *Neurology*. 2014;82(21):1856-61.
2. Dauvilliers Y, Winkelmann J. Restless legs syndrome: update on pathogenesis. *Current opinion in pulmonary medicine*. 2013;19(6):594-600.
3. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. *European neurology*. 2000;43(2):70-5.
4. Rajaram SS, Rudzinskiy P, Walters AS. Enhanced external counter pulsation (EECP) for restless legs syndrome (RLS): preliminary negative results in a parallel double-blind study. *Sleep medicine*. 2006;7(4):390-1.
5. Kanter AH. The effect of sclerotherapy on restless legs syndrome. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 1995;21(4):328-32.
6. Driver-Dunckley E, Evidente VG, Adler CH, Hillman R, Hernandez J, Fletcher G, et al. Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. *Movement disorders : official journal of the Movement Disorder Society*. 2006;21(8):1287-9.
7. Hu J. Acupuncture treatment of restless leg syndrome. *Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese Medicine*. 2001;21(4):312-6.
8. Burbank F, Buchfuhrer M, Kopjar B. Sleep improvement for restless legs syndrome patients. Part I: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013:1-10.
9. Allen RP, Picchiatti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep medicine*. 2003;4(2):101-19.
10. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep medicine*. 2003;4(2):121-32.
11. Pan W, Wang M, Li M, Wang Q, Kwak S, Jiang W, Yamamoto Y. Actigraph evaluation of acupuncture for treating restless legs syndrome. *Evid Based Complement Alternat Med*. 2015;2015:343201. doi: 10.1155/2015/343201. Epub 2015 Feb 11. PubMed ID: 25763089

- 12.Cripps MG. Acupuncture for restless legs syndrome in patients previously treated with dopaminergic drugs. *Acupunct Med.* 2011 Sep;29(3):240-1.
- 13.Yıldız A, Yıldız C, Karakurt A. Assessment of cardiac autonomic functions by heart rate variability in patients with restless leg syndrome. *Turk Kardiyol Dern Ars.* 2018 Apr;46(3):191-196.
- 14.Raissi GR, Forogh B, Ahadi T, Ghahramanpoori S, Ghaboussi P, Sajadi S. Evaluation of Acupuncture in the Treatment of Restless Legs Syndrome: A Randomized Controlled Trial. *J Acupunct Meridian Stud.* 2017 Oct;10(5):346-350. doi: 15.1016/j.jams.2017.08.004. Epub 2017 Aug 22. Erratum in: *J Acupunct Meridian Stud.* 2018 Dec;11(6):380.
- 16.Barone DA, Ebben MR, DeGrazia M, Mortara D, Krieger AC. Heart rate variability in restless legs syndrome and periodic limb movements of Sleep. *Sleep Sci.* 2017 Apr-Jun;10(2):80-86. doi: 10.5935/1984-0063.20170015.
- 17.Cikrikcioglu MA, Hursitoglu M, Erkal H, Kinas BE, Sztajzel J, Cakirca M, Arslan AG, Ereğ A, Halac G, Tukek T. Oxidative stress and autonomic nervous system functions in restless legs syndrome. *Eur J Clin Invest.* 2011 Jul;41(7):734-42. doi: 10.1111/j.1365-2362.2010.02461.x. Epub 2011 Jan 20.